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Outcomes of Stavudine-Associated Peripheral Neuropathy in HIV-Infected Individuals in Rural Uganda

G. Mwima[1], D. Moore[1,2,3], W. Were[1], S. Malamba[1], J. Mermin[1], P. Weidle[4], F. Asiimwe[1], F. Forna[1], B. Waiswa[1], A. Barasa[1], A. Mubiru[1], J. Tappero[1]

Centers for Disease Control and Prevention (CDC), Global AIDS Program, Entebbe Uganda[1], British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada[2], Dept. of Medicine, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada[3] Division of HIV/AIDS Prevention, National Center for HIV, STD and TB prevention, CDC, Atlanta, GA, USA[4]

Contact address:
gmwima@ug.cdc.gov
Phone: ++256-772-762722
Fax: ++256-414-321457
Mailing address: P.O. Box 49
Entebbe, Uganda

Abstract

Background: Stavudine is a commonly used component of ART regimens in resource-limited settings, despite its known risk of peripheral neuropathy. We assessed the long term clinical course of stavudine-associated neuropathy in Uganda

Methods: Study participants initiated home-based ART as part of a randomised clinical trial of different ART monitoring strategies. We diagnosed stavudine-associated neuropathy using standardized criteria. Those with severe or persistent neuropathy were switched to zidovudine. We used logistic regression analysis to examine factors associated with improvement.

Results: A total of 860 adult ART-naïve participants began stavudine-containing ART and 306 (36%) reported symptoms of peripheral neuropathy. All received supportive treatment for neuropathy. We assessed 296 (96%) of these patients after a median of 20.5 months to re-evaluate neuropathy. Among 143 (48%) who remained on stavudine 77 (54%) improved, 58 (40%) were unchanged and 8 (6%) worsened. Fifty-two percent (153) switched to zidovudine and 115 (75%) showed improvement while 30 (20%) were unchanged and 3 (2%) worsened. In multivariate analysis baseline CD4 cell count >200/mm3 (adjusted odds ratio [AOR] 3.32, 95% (CI): 1.03-10.7) was associated with subsequent improvement among those who switched. Reported isoniazid exposure at baseline was associated with reduced odds of improvement (AOR = 0.34, 95% CI: 0.11-1.05)

Conclusions: For people with mild symptoms of stavudine-associated peripheral neuropathy, improvement of one grade or more was common without drug substitution. For people with severe or persistent neuropathy, most improved after a single drug substitution from stavudine to zidovudine, although improvement was more likely among those with higher baseline CD4 cell counts.

Study physician performing neurological assessment of participant

Field officer administering questionnaire at home to study participant

Background

- In 2003, WHO recommended either stavudine or zidovudine in combination with lamivudine plus a NNRTI as first line ART regime in resource-limited settings
- The 2006-2007 WHO updated guidelines still allow use of 30mg of stavudine but not as a preferred drug
- Stavudine is cheap but has been associated with adverse events, commonly peripheral nueropathy, lactic acidosis and lipodystrophy
- Stavudine is likely to remain a commonly prescribed component of ART in sub-Saharan Africa
- A previous study in the Home-Based AIDS Care Project in Uganda (HBAC), stavudine-related neuropathy was the most common reported adverse event of ART
- We assessed the long term clinical course of stavudine-associated neuropathy and examined associations with improvement

Methods

Study location: Tororo District, Uganda

Study period: May 2003-December 2004 and June-August 2006

Study design: Prospective cohort study

Enrolment: All adult participants diagnosed with peripheral neuropathy between May 2003 and December 2004. We excluded participants who were either HAART-experienced or had neuropathy at baseline.

Follow-up: Re-evaluation was done between June-August 2006 by the same physician

Data collection: Neuropathy symptoms were documented through a weekly field questionnaire. Neuropathy was evaluated and graded by study physicians during clinic visits. Re-evaluation and grading of neuropathy was done between June-August 2006.

Statistical methods: Wilcoxan rank Sum test was used to compare improvement in neuropathy grade. For those with a single drug substitution to zidovudine, we used logistic regression analysis to examine factors associated with improvement. We used Akaike's Information Criteria to determine the final multivariate model.

Results

Of 860 participants initiated on stavudine-containing ART regimens, 308 (35%) reported symptoms of neuropath y within a median of 28 days after ART initiation.

We evaluated 296 (96%) of those who developed neuropathy with a repeat assessment at a median of 20.5 months after initial diagnosis. Of the 143 maintained on stavudine (77 (54%) showed improvement, 58 (40%) had no change, 8 (6%) worsened). One hundred fifty three participants (51.7%), had a single drug substitution to zidovudine and 115 (75%) showed improvement, 30 (20%) had no change and 3 (2%) worsened.

In the logistic regression analysis for those who had a single drug substitution to zidovudine, baseline CD4 cell count ≥200 cells/mm³ (odds ratio [OR] = 2.59; 95% confidence interval [CI] 0.84 – 7.98) was associated with improvement

Baseline alcohol consumption (OR = 0.47; 95% CI 0.17 – 1.3) and isoniazid exposure at baseline (OR = 0.36; 95% CI 0.12 - 1.0) were inversely associated with improvement.

In the final multivariate logistic regression, only baseline CD4 cell count ≥ 200/mm³ (Adjusted odds ratio [AOR] 3.32; 95%CI 1.03 – 10.7) was associated with improvement. Isoniazid exposure was marginally associated with a reduced odds of improvement (AOR = 0.34, 95% CI: 0.11 – 1.05)

Table 2: Logistic regression analysis for factors associated with improvement in Neuropathy grading for 153 participants switched to zidovudine

Variables	Univariate Odds ratio (95% CI)	P value	Multivariate Odds (95% CI)	P value
Gender				
Female	0.69 (0.26-1.84)	0.460		
Male	1.00			
Age per years	0.98 (0.93-1.02)	0.318		
BMI (Kg/m^2)				
<18	0.78 (0.31-1.96)	0.598		
⩾18				
CD4 Stratified			3.32 (1.03-10.7)	0.044
⩾ 200	2.59 (0.84-7.98)	0.098	1.00	
< 200	1.00			
Alcohol consumption			0.423 (0.14-1.23)	0.115
Yes	0.47 (0.17-1.31)	0.149	1.00	
No	1.00			
Assessment interval/ months	0.85 (0.39-1.87)	0.693		
Isoniazid Exposure	0.358 (0.12-1.01)	0.073	0.33 (0.11-1.05)	0.061
D4T Dose				
40mg	1.00	0.404		
30mg	1.43 (0.62-3.28)			
D4T Exposure per month	1.00 (0.99-1.00)	0.2400		

Table 1: Baseline characteristics of 860 ART-naïve participants

Characteristic	No neuropathy	Developed neuropathy	p-values
Number N (%)	552 (64.2%)	308 (35.8%)	
Female	388 (70.3%)	242 (78.6%)	0.009
Male	164 (29.7%)	66 (21.4%)	
Age in years	37 (32-42.2)*	40.0 (35-45.5)	0.001
BMI (Kg/M^2)	19 (18-21.4) *	20.05 (18.37-22.0)	0.008
CD4 cell count/µl)	128 (69-193) *	130 (74-191.5)	0.125
Median Viral load (Copies per ml, '000)	214 (73-525) *	220 (78-572)	0.392
Hemoglobin (g/dL)	11.2 (10.1-12.5) *	11.5 (10.2-12.5)	0.196
Evidence of alcohol consumption	98 (17.8%)	44 (14.3%)	0.213

* Median (IQR interquartile range)

Discussion

- Substituting stavudine with zidovudine improves moderate to severe peripheral neuropathy in participants.
- Most patients with mild peripheral neuropathy maintained on stavudine generally improved or did not progress.
- Isoniazid exposure was marginally associated with decreased odds of improvement; consistent with it's known neurotoxicity. A previous study in this cohort showed isoniazid exposure contributed to development of neuropathy.
- Patients with higher CD4 cell counts were more likely to improve. Early substitution to zidovudine in patients with lower CD4 cell counts or TB treatment may result in less persistent neuropathy
- While stavudine is no longer recommended as a first line NRTI, it may continue being used as part of ART for patients in resource limited settings given its cost
- Limitations: Small numbers may have limited our ability to examine risk factors for improvement and the participants who received or did not receive zidovudine were not comparable. However since we found an effect even though only the severely affected group had a switch, there is substantial evidence of efficacy. This study examined only peripheral neuropathy whereas other side effects may limit the use of stavudine

Conclusions

- **The most common side effect associated with stavudine use, peripheral neuropathy, is largely reversible after switching to zidovudine**
- **Programmatically, stavudine may continue to be the most suitable alternative for the near future in this setting given it's low cost**
- **ART programs in resource-limited settings can consider starting patients on stavudine and substituting with zidovudine if neuropathy develops as this appears to be a safe and cost-effective strategy for ART delivery**